REMARKS

Claims 22-30 and 32-58 are pending. Claim 31 has been cancelled as it discloses the same compound as is claimed in Claim 32. Support for the amendments to Claims 22, 30 and 42 can be found in the specification at page 2, line 1, through page 3, line 19; page 11, line 5 through page 12, line 23; and at page 20, line 8 through page 21 line 6. Support for new Claim 49 is found in pending claim 31, and support for new claims 50-58 is found in pending claims 33-41, respectively.

The claim amendments are presented in a revised format per the USPTO's announcement 'Amendments in a Revised Format Now Permitted', signed 31 January 2002, and accordingly do not conform to the current reading of 37 C.F.R. §1.121, which Applicant understands has been waived. Accordingly, a complete listing of all claims that are, or were in the application, along with an appropriate status identifier, is provided above in the section entitled "Amendments to the Claims".

Rejections under 35 U.S.C. § 112, second paragraph

Claims 30-48 are rejected under 35 U.S.C. § 112, second paragraph for being indefinite. Specifically Claims 30 and 42 are rejected for lack of clarity due to the use of the word "rapid". Claims 30 and 42 have been amended for technical clarity by replacing the phrase "such that the rapid exchange of water in at least one coordination site of said agent is increased" with the phrase "such that the T_1 of the agent is decreased." Applicants submit that the use of this phrase will be understood by a person of skill in the art to mean that the measured relaxivity of the complex is increased, thereby resulting in an enhancement in the MRI signal.

Applicants respectfully request withdrawal of the rejection of Claims 30 and 42 under 35 U.S.C. § 112, second paragraph.

Claim 32 is rejected because it does not contain a period. Applicants have amend Claim 32 to include a period. Accordingly, Applicants respectfully request withdrawal of the rejection of Claim 32 under 35 U.S.C. § 112, second paragraph.

Claim 42 is rejected because for lack of clarity due to the use of the phrase "therapeutic effect is elicited". Claim 42 has been amended to omit this phrase. Accordingly, Applicants respectfully request withdrawal of the rejection of Claim 42 under 35 U.S.C. § 112, second paragraph.

Claims 32 to 40 are rejected because a dependent claim must refer to a preceding claim. Claims 32 to 40 have been amended to depend from a preceding claim. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 32 to 40 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102(e)

Claims 22-24, 28 and 29 are rejected under 35 U.S.C. § 102(e) as being anticipated by Piwnica-Worms, U.S. Patent No. 6,348,185 (hereinafter referred to as the '185 patent).

As a preliminary matter, Applicants respectfully point out that pending claims 22, 25-33, 36-50, and 53-58 have a priority date based on U.S.S.N. 08/971,855, which was filed on November 17, 1997. Support for the MRI agents disclosed in claims 22, 30, 32, and 42 can be found at least at page 12, lines 24-25, page 22, line 6 through page 23, line 10, page 25, lines 7-15, and page 30, line 12 through page 31, line 6 of the priority document. Support for the MRI agents disclosed in claims 25-29, 33, 36-41, 43-50 and 53-58 can be found at least at page24, line 21, through page 25, line 1. Thus, the '185 patent is not 102(e) art against claims 22, 25-33, 36-50 and 53-58. Accordingly, Applicants respectfully request that the rejection against claims 22, 28 and 29 be withdrawn.

With respect to claims 23, 24, 34 and 35, Applicants respectfully disagree that these claims are anticipated under 35 U.S.C. § 102(e) by the '185 patent. As the Examiner has indicated, the '185 patent is directed to MRI agents comprising the following components: a peptide linked via a linker to a chelate-metal complex (see Column 18, lines 32-40). As noted at Column 19, lines 17-27, the MRI image obtained using the agents of the '185 patent is due to the inherent properties associated with using a relaxivity metal, such as Gd. However, the '185 patent does not disclose that any of the other components of the MRI agent complex can be used to further enhance the MRI image over that obtained using Gd alone.

In contrast, Claims 23, 24, 34 and 35 are directed to MRI agents comprising a DOTA chelate, a paramagnetic ion, a linker, and a peptide blocking moiety. Upon interaction of the peptide blocking moiety with a target substance, the peptide dislodges from the coordination site of the metal such that the T_1 of the agent is decreased, thereby resulting in an enhanced MRI image. Thus, the MRI agents disclosed in Claims 23, 24, 34 and 35are activatible, i.e., capable of being turned "on" and "off" through the interaction of the peptide moiety with its target substance.

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

As can be seen from the above discussion, there is no disclosure in the '185 patent regarding an MRI agent comprising a component that is capable of turning on the agent via an interaction with a target substance such that the T1 of the agent is decreased.

Therefore, the '185 patent does not teach or suggest each and every element of the claimed invention. Accordingly, Applicant respectfully submits the rejection under 35 U.S.C. § 102(e) does not apply to claims 23, 24, 34 and 35.

Rejection under 35 U.S.C. § 103(a)

Claims 22, 25-27 and 30-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the '185 Patent.

As stated above, pending claims 22, 25-33, 36-50, and 53-58 have a priority date based on U.S.S.N. 08/971,855, which was filed on November 17, 1997. Thus, the '185 patent is not 103(a) art against claims 22, 25-33, 36-50 and 53-58. Accordingly, Applicants respectfully request that the rejection against claims 22, 25-27 and 30-33 and 36-48 be withdrawn.

Moreover, Applicants respectfully disagree that Claims 22, 25-27 and 30-48 are unpatentable under 35 U.S.C. § 103(a) by the '185 patent and with the Examiner's definition of what constitutes an activatible complex. An activatible complex, as disclosed in the present invention is a complex that is capable of being turned on (i.e., the T_1 of the agent is decreased) and off (i.e., the T_1 of the agent is increased) via the interaction or lack thereof between a blocking moiety and a target substance. Accordingly, an activatible agent "is not any agent used for imaging that targets a specific location and generates an image" (see page 8, first paragraph of the office action).

The '185 patent and the present invention have been discussed above.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make

the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

As argued above, the '185 patent does not teach or suggest all of the claim limitations. In particular, there is no disclosure in the '185 patent regarding an MRI agent comprising a component that is capable of turning on the agent via an interaction with a target substance such that the T_1 of the agent is decreased.

Therefore, the requirement of teaching or suggesting all the claim elements has not been met. Applicant respectfully submits the rejection under 35 U.S.C. § 103(a) does not apply to claims 22, 25-27 and 30-33 and 36-48.

Claims 22 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gries et al., U.S. Patent No. 5,648,063.

Gries discloses agents for use in NMR and X-ray diagnosis comprising complex salts and a paramagnetic ion to which biomolecules such as peptides and antibodies may be conjugated (see column 3, line 43 through column 4, line 7). As noted by the Examiner, Gries does not disclose MRI agents comprising a DOTA chelate, a paramagnetic ion, a linker, and a peptide blocking moiety. Furthermore, as argued above, the Examiner's definition of an activatible agent is not supported by Applicant's disclosure.

Claims 22 and 32 are directed to MRI agents comprising a DOTA chelator, a paramagnetic ion, a linker, and a peptide blocking moiety and methods of using these agents. As discussed above, upon interaction of the peptide blocking moiety with a target substance, the peptide dislodges from the coordination site of the metal such that the T_1 of the agent is decreased, thereby resulting in an enhanced MRI image. Thus, the MRI agents disclosed in

Claims 22 and 32 are activatible, i.e., capable of being turned "on" and "off" through the interaction of the peptide moiety with its target substance.

The law under 35 U.S.C. § 103(a) has been summarized above.

As argued above, Gries does not teach or suggest all of the claim limitations. In particular, there is no disclosure in the Gries regarding an MRI agent comprising a component that is capable of turning on the agent via an interaction with a target substance such that the T_1 of the agent is decreased.

Therefore, the requirement of teaching or suggesting all the claim elements has not been met. Applicant respectfully submits the rejection under 35 U.S.C. § 103(a) does not apply to claims 22 and 32.

Claims 22-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gries et al., U.S. Patent No. 5,648,063 in view of Piwnica-Worms, U.S. Patent No. 6,348, 185.

As stated above, pending claims 22, 25-33, 36-50, and 53-58 have a priority date based on U.S.S.N. 08/971,855, which was filed on November 17, 1997. Thus, the '185 patent is not 103(a) art against claims 22, 25-33, 36-50 and 53-58. Accordingly, Applicants respectfully request that the rejection based on Gries in view of the '185 patent does not apply against these claims and that the rejection be withdrawn.

Gries, the '185 patent, the pending claims, and the law under 35 U.S.C. § 103(a) have been discussed above.

As argued above, none of the prior art, alone or in combination, discloses each of the claimed elements. There is no teaching or suggestion in either Gries or the '185 patent regarding an MRI agent comprising a component that is capable of turning on the agent via an interaction with a target substance such that the T_1 of the agent is decreased.

Therefore, the requirement of teaching or suggesting all the claim elements has not been met. Applicant respectfully submits the rejection under 35 U.S.C. § 103(a) does not apply to claims 22-32.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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